Remarks

Claims 58-83 are pending in the subject application. By this Amendment, Applicants have canceled claims 58-83, and added new claims 84-124. Support for the new claims can be found throughout the subject specification and in the claims as originally filed and New (see, for example, paragraphs 3, 11-19, 53 and paragraphs 74-104 and the original claims of published U.S. Patent Application Publication US 2002/0192644 A1). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 84-124 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Applicants thank the Examiner for the courtesy of the interview of September 8, 2004 in which the current application was discussed. Applicants have included a Statement of Substance of Interview Under 37 C.F.R. § 1.333 with this response and incorporate its contents into this response in their entirety.

Claims 58-83 are rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully submit that this rejection is moot in view of the amendments made to the claims, accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Applicants note that the Office Action has posited that one is to have "oligonucleotides" (probes) hybridize to nucleic acid that encodes any of immunoreceptors p58.1, p58.2, p70, INH, p140.NH, NKG2A, and NKG2B, but does not hybridize with any nucleic acid that encodes a "NKR activatory immunoreceptor." The Office Action further indicates that the names "p58.1, p58.2, p70.INH, p140.NH, NKG2A, and NKG2B" are of proteins, and that the specification does not teach the amino acid sequence of each of these proteins, or equivalents as found in any life form, nor does the specification teach the nucleotide residue sequence is for same. The Office Action also argues that the specification has not provided an adequate written description of any and all nucleic acids that encode a "NKR activatory immunoreceptor" and that Applicant has indicated how unnamed proteins are to function (*i.e.*, NKR activatory immunoreceptor), however, such language does not provide an adequate written description of the nucleic acids to which the oligonucleotide pairs are not to hybridize.

Applicants respectfully submit that the specification does, indeed, provide teachings related to the cDNA sequences of these known NKR immunoreceptors and how oligonucleotide probes are to be obtained such that they hybridize with a target immunoreceptor sequence but not to a counterpart immunoreceptor sequence (see, in particular paragraph 83 of U.S. Patent Application Publication US 2002/0192644 A1). As the specification indicates, oligonucleotide probe pairs were obtained by alignment of known cDNA NKR target immunoreceptor sequences (see paragraphs 81-87 of U.S. Patent Application Publication US 2002/0192644 A1). As is also discussed therein, consensus sequences of the target receptor or its counterpart receptor were developed from the GenBank sequences identified in Table 2. Thus, cDNA sequences of various target and counterpart receptors were disclosed in the as-filed specification and Applicants have provided adequate written description of the reagents to be used in the practice of the invention.

Furthermore, Applicants respectfully submit that cDNA sequences of target and counterpart NKR receptors would have been known and readily available to those skilled in the art related to natural killer cells and NKR receptors at the time the application was filed. For example, the GeneCard database (worldwide website bioinfo:weizmann.ac.il/cards/index.shtml) was available to those skilled in the art. This database would have allowed, and allows, for the accession of various cDNA sequences associated with a particular human gene as well as the identification of various names (aliases and descriptions) associated with a given GenBank Accession Number. As an illustration, the GeneCard printout for GenBank Accession No: U24076 is attached hereto. As the Patent Office will note, one of the aliases or descriptions of the cDNA of the accession number is p58.1, thus it is respectfully submitted that one skilled in the art would have been able to readily practice the invention in view of the teachings of the specification related to NK cells and the receptors thereof and the knowledge of those skilled in the relevant art. Additionally, it is respectfully submitted that a search of the designations p58.1, p58.2, p70, p140, etc. in conjunction with the terms "natural" and "killer" identified a number of review articles discussing NKR receptors and their activities in the National Library of Medicine PubMed database. Likewise, a search of the GenBank Accession No: U24076 identified a number of review articles discussing various NKR immunoreceptors in the National Library of Medicine PubMed database. Accordingly, it is respectfully submitted that the NKR immunoreceptors identified in the specification would have

been well known to those skilled in the art at the time the invention was made and that an adequate written description of these immunoreceptors, as well as their amino acid and cDNA sequences was provided in the as-filed application (particularly in view of the teachings of the specification and Tables 1-2).

The Office Action also argues that the specification fails to provide an adequate written description of how the detection of any one or combination of nucleic acid sequences encoding any portion of immunoreceptors p58.1, p58.2, p70.INH, p140.INH, NKG2A and NKG2B is to be extrapolated so that a skilled artisan would be able to practice a variety of intended uses identified in claims 62-65, 67 and 77-80. While this issue is now moot in view of the cancellation of the claims, Applicants respectfully traverse.

The specification discusses NKR receptors (*e.g.*, KIR (Killer Cell Inhibitory Receptors) receptors, lectin-type NKR receptors, and KAR (Killer Cell Activatory Receptors) receptors and their function in paragraphs 3-10 of U.S. Patent Application Publication US 2002/0192644 A1. As set forth therein, NKR receptors and NKR receptor counterparts are expressed on the surfaces of NK cells and T-cell subpopulations and these receptors recognize MHC Class I molecules as ligands. Recognition of the ligand by the NKR receptor (*e.g.*, a KIR receptor) inhibits the activity of the NK cell (*e.g.*, it does not initiate the cascade of events that causes the cytolysis of the target cell). However, if the NKR receptor counterpart (*e.g.*, KAR receptors) binds to the ligand, the cell is activated (or not inhibited) and the cascade of events that causes the cytolysis of the target cell is initiated.

It is also respectfully submitted that the types of events in which these receptors are involved known in the art. As discussed in Cantoni *et al.* (Chem. Immunol., 1996, 64:88, paragraph 1 [a review article directed to NK cell receptors]), NK cells play an important role in cell-mediated immune responses to tumor or virally-infected cells. NK receptors specifically recognize HLA Class I molecules (HLA-A, HLA-B, and HLA-C) and NK activity is regulated by these receptors. Normal cells expressing self HLA Class I molecules are not killed by autologous NK cells whereas cells failing to express self MHC molecules (HLA-A, HLA-B, or HLA-C) are killed. Thus, cells, such as cancer cells or virally infected cells, failing to express a MHC Class I molecule (or expressing the improper MHC Class I molecule) are killed.

As set forth in the specification, the subject invention allows those skilled in the art to document the NKR receptor repertoire of an individual. Armed with this knowledge, one is able to: 1) better match (and predict acceptance of) organs to be transplanted since one would know the receptor repertoire of the NK cells tasked with distinguishing self from non-self (*e.g.*, match organs having the appropriate HLA phenotype on the cell surface to be transplanted into an individual that has a particular NKR immunoreceptor repertoire and thereby reduce the risk of organ rejection); 2) predict the possibility of GVH based on the NKR repertoire and the HLA phenotype of transplanted cells; or 3) identify those individuals to be monitored for the possible appearance of GVH or organ/tissue rejection based on the NKR receptor repertoire of the individual and the HLA phenotype of the transplanted cells or organ/tissue. With respect to the issue as raised with respect to GVL (graft versus leukemia), Albi *et al.* (Blood, 1996, 87(9):3993-4000; cited in paragraph 7 of the published application) discuss the phenomenon noted with respect to NK cells transplanted into HLA-mismatched individuals. As would be known to one skilled in the field of NK cells and their receptors, $CD3^+/CD8^+$ lymphocytes expressing p58 NKR receptors undergo a long-lasting expansion in HLA-incompatible recipients having acute leukemia. These same cells are able to lyse leukemia cells (cells lacking HLA molecules), but not normal cells expressing HLA molecules. Thus, the subject invention would allow one to predict the potential effect GVL effect of a bone marrow transplant from a donor into a HLA-mismatched leukemic patient since the NKR receptor repertoire of the donor would be known (*e.g.*, cells expressing p58).

Paragraph 9 of the Office Action appears to argue that there is no written support for claims directed to oligonucleotides are coupled to a marker. Applicants respectfully submit that support for such a claim can be found in the published application at paragraph 53 (discussing coupling of 5' or 3' oligonucleotides to radioactive or fluorescent markers) and original claim 23 of U.S. Patent Application Publication US 2002/0192644 A1.

Claims 58-83 are also rejected under 35 USC §112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is respectfully submitted that this

rejection is moot in view of the cancellation of the claims. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 62-67 and 77-80 are rejected under 35 USC §112, second paragraph and are rejected under 35 U.S.C. §101. While it is respectfully submitted that the claims were definite and have patentable utility, the cancellation of the claims has rendered this issue moot. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No: 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Frank C Eisenschenk

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No: 45,332
Phone No: 352-375-8100
Fax No: 352-372-5800
Address: Saliwanchik, Lloyd & Saliwanchik
A Professional Association
P.O. Box 142950
Gainesville, FL 32614-2950

FCE/ssa

Attachments: Statement of Substance of Interview Under 37 C.F.R. § 1.133
Copy of GeneCard printout for GenBank Accession No: U24076
Copy of Cantoni *et al.* (Chem. Immunol., 1996, 64:88)
Copy of Albi *et al.* (Blood, 1996, 87:3993)

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313 on October 14, 2004.

Frank C. Eisenschenk

Frank C. Eisenschenk, Ph.D., Patent Attorney

STATEMENT OF SUBSTANCE OF INTERVIEW
Examining Group 1634
Patent Application
Docket No. INN-113T
Serial No. 09/529,759

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Bradley L. Sisson
Art Unit	:	1634
Applicants	:	Eric Vivier, Frederic Vely
Serial No.	:	09/529,759
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Confirm. No.	:	9965
For	:	Documentation Means for Repertoires of NKR Immunoreceptors and/or Activatory or Non-Inhibitory Immunoreceptor Counterparts of NKR Immunoreceptors

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT OF SUBSTANCE OF INTERVIEW UNDER 37 C.F.R. §1.133

The applicants wish to thank Examiner Sisson for the courtesy of the telephonic examiner interview conducted on September 8, 2004 with the undersigned. The remarks set forth in the Interview Summary Form that accompanied the Office Communication dated September 13, 2004 are consistent with the substance of that interview. Applicants submit, herewith, additional comments with respect to the interview.

With respect to the specific points mentioned in the Interview Summary, the undersigned inquired as to the possibility of providing a substitute sequence listing providing the nucleic acid sequences identified by GenBank Accession No. in Table 2 of the subject application and correlation of these sequences with the NKR immunoreceptors associated therewith (as identified in Table 1). As was also discussed, the Genbank sequences are present in publicly accessible databases.

The issue with respect to the phrase "or a sequence derived therefrom" in claim 58, steps (b), (c), and (d) was also discussed; it is believed that this issue is now moot in view of the cancellation of the claim.

With respect to the issue raised in the Office Action with respect to the lack of written description for oligonucleotides labeled with a marker, Applicants respectfully submit that such labeled oligonucleotides are specifically taught in the application as originally filed (see, for example, paragraph 53 and claim 23 of U.S. Patent Application Publication US 2002/0192644 A1.

Applicants are in the process of attempting to obtain a declaration related to the nomenclature of NKR immunoreceptors and have, in the interim, provide a review article discussing the same in an effort to assist the Examiner.

Applicants invite the Examiner to call the undersigned if clarification is needed with respect to this paper, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: Saliwanchik, Lloyd & Saliwanchik
A Professional Association
P.O. Box 142950
Gainesville, FL 32614-2950

FCE/ssa